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Electroconvulsive Shock and Neurotransmitter Receptors: Implications for Mechanism of Action and Adverse Effects of Electroconvulsive Therapy[1]

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Neurochemical effects of electroconvulsive shock (ECS) in three neurotransmitter-receptor systems were studied in relation to the mechanism of action and adverse effects of ECT. In the noradrenergic system, chronically administered ECS, along with other effective antidepressant treatments, has been consistently reported to down-regulate β-adrenergic receptors in rat cerebral cortex. Even when ECS was administered according to an intermittent clinically equivalent schedule, a 21% reduction in cortical ^{3}H-DHA binding to β-adrenoreceptors could be demonstrated 4 days after the last treatment. However, the role of presynaptic NA events in β-adrenoreceptor down-regulation by ECS and the antidepressant mechanism of ECT remains to be clarified. Compared to the MAO inhibitor clorgyline, repeated ECS pretreatment induced only a moderate increase in NA release from a rat cortical vesicular preparation and minimally reduced the sensitivity of the preparation to release-inhibition by clonidine. In the dopaminergic system, a clinically equivalent ECS schedule had no direct effect on behavioral or biochemical indices of DA receptor sensitivity. However, the same ECS schedule significantly attenuated haloperidol-induced behaviorally and biochemically measured DA supersensitivity in the same model in which parallel

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effects had been reported for lithium. The possibility that a "receptor-stabilizing" mechanism may be common to ECT and lithium is considered on the basis of similarities in the clinical profiles of the two treatments. In the cholinergic system, repeated ECS significantly reduced ^{3}H-QNB binding to muscarinic cholinergic receptors in rat cerebral cortex and hippocampus. Concurrently administered ECS also blocked the increase in ^{3}H-QNB binding caused by chronic atropine administration. ECS effects on muscarinic cholinergic receptors may have relevance to the antidepressant mechanism of ECT. Their possible relationship to ECT-induced memory impairment is of particular interest. ECS effects on all three neurotransmitter receptor systems studied represent viable approaches to defining the mechanism of action of ECT and those in the acetylcholine system may be relevant to our understanding of the neurochemical basis of ECT-induced amnesia. Further studies are needed to critically test the hypothesis advanced.

INTRODUCTION

Electroconvulsive therapy (ECT) has played a central role in psychiatric treatment for almost 50 years. In spite of advances in antidepressant medication, ECT is still a mainstay in the clinical management of severe depressive illness. Yet the basic mechanisms which underlie the therapeutic efficacy of ECT remain unclear. The biological basis of ECT-induced memory impairment, the major adverse effect of anesthetic- and muscle-relaxant modified ECT, is also not known. Public controversy regarding the use of ECT is undoubtedly influenced by the empirical nature of the treatment and its effect on memory. An explanation might make it possible to ultimately replace ECT with a treatment as thera- or treat ECT-induced amnesia could considerably defuse public concern. Moreover, our understanding of the biological basis of affective disorder might be advanced considerably by an explanation of ECT mechanisms. Such an explanation might make it possible to ultimately replace ECT with a treatment as therapeutically effective but devoid of controversial aspects and troublesome adverse effects.

Research into the mode of action of ECT provides a unique opportunity for understanding antidepressant mechanisms in general since findings are not influenced by pharmacokinetic considerations. Moreover, the demonstration that a particular mechanism is common to treatments as different in their nature as ECT and the chemical antidepressants could provide strong theoretical support for the putative role of such a mechanism in alleviating depressive symptoms. Recent theories of affective disorder have emphasized neurotransmitter receptors as mediators of pathogenesis and treatment (Bunney *et al.*, 1977). Much recent research on the mechanism of action of ECT has stressed alterations

in receptor sensitivity induced by repeated electroconvulsive shock (ECS) as measured by behavioral or radioligand-binding techniques (Lerer *et al.*, 1983a; Lerer and Belmaker, 1982; Grahame-Smith *et al.*, 1978).

The present paper focuses on changes in receptor sensitivity induced by repeated ECS in the noradrenergic, dopaminergic, and cholinergic systems. The relationship of these changes to presynaptic events is evaluated and their possible relevance to the antidepressant action and amnestic effects of ECT is considered. Possible parallels between the mechanism of action of ECT and that of lithium are also discussed. The approach taken in defining the clinical implications of ECS-induced effects is that suggested by Kety (1974) and Grahame-Smith *et al.* (1978). Findings are therefore regarded as having greater relevance to clinical ECT mechanisms if they are demonstrable after chronic but not single ECS, are clearly not due to nonspecific handling effects ("sham ECS" control group), and are relatively persistent and not due to the acute effects of the last of a series of ECS administrations.

METHODS

Male albino rats (Sprague-Dawley or Sabra strain) weighing 150-200 g were used in all experiments. Animals were group-housed in identical wire or plastic cages in a temperature controlled (24 C) environment with a regular 12-hr light-dark cycle. Food and water were available ad lib.

Electroconvulsive shock (130-150 V, for 0.75-1.0 sec) was administered via earclip electrodes from a clinical ECT apparatus (Duopoulse or Medcraft). This stimulus was regularly observed to induce a generalized tonic-clonic seizure lasting 20-30 sec, followed by a brief (1 to 2-min) period of postictal stupor, with full recovery within a few minutes. The ECS regimen used was either single ECS, one ECS daily for 7-10 days, or ECS thrice weekly for 4 weeks. Control animals received sham ECS which involved identical handling procedures with application of earclip electrodes but no current. Animals were killed by decapitation 24 hr or 7 days after single ECS and 24-96 hr after the last of a series of ECS.

Drugs were administered either as intraperitoneal (ip) injections or thoroughly mixed into finely ground rat chow. Control animals received either ip injections of the appropriate vehicle or identical ground food without the added medication. Details of drug treatments and dosages are given under each of the experiments discussed.

Behavioral observations were performed in a semidarkened room by an observer blind to the treatment status of the animals. Animals were rated in balanced groups so that one animal from each treatment possibility was simultaneously observed and scored.

Biochemical studies were performed on specimens of rat brain which were rapidly dissected immediately after decapitation. Noradrenaline (NA)-release studies were performed on fresh vesicular preparations on the same day. Tissues for receptor binding studies were frozen at −70° C until assay.

All data were analyzed with a Student's *t* test (two-tailed) unless otherwise specified.

ECS AND β-ADRENERGIC RECEPTORS

Down-Regulation of β-Adrenergic Receptors by Clinically Equivalent ECS S

Previous reports had shown that ECS administered daily for 7-10 days induced a significant 25-27% decrease in [^{3}H]dihydroalprenolol (^{3}H-DHA) binding ing to cortical β-adrenergic receptors (Bergstrom and Kellar, 1979; Pandey *et al.*, 1979). This finding was replicated in our studies (Birmaher *et al.*, 1982) which showed a significant reduction in ^{3}H-DHA binding following daily ECS for 10 days. In the clinical setting, however, ECT is administered according to a spaced schedule (2-3 times per week) rather than on a consecutive daily basis. It was therefore of interest to determine whether ECS administered to rats according to a clinically equivalent schedule would induce a similar down-regulation of β-adrenergic receptor number. Rats were administered ECS thrice weekly for 4 weeks and killed 96 hr after the last treatment (Belmaker *et al.*, 1982). Cortical β-adrenergic receptor number was determined by ^{3}H-DHA binding according to the method of Bylund and Snyder (1976).

ECS induced a 21% reduction in β-adrenergic receptor number (Bmax) with no change in affinity (Kd). This effect was statistically significant and of the same order of magnitude as the change induced by 7-10 daily ECS (Bergstrom and Kellar, 1979; Pandey *et al.*, 1979). It is of interest to note that this finding was demonstrable 4 days after the last ECS. Keller *et al.* (1981) had reported that following 7 daily ECS, significant down-regulation of β-adrenergic receptors was still present 7 days after the last treatment. The above finding shows similar persistence of the ECS effect even after a more clinically equivalent schedule. Our studies on the effects of ECS on NA release were directed at exploring the possible role of presynaptic NA mechanisms in mediating the above postsynaptic effects and in the antidepressant action of ECT.

Effect of ECS on NA Release

ECS exerts considerable effects on mechanisms mediating presynaptic availability of NA. Repeated ECS has been found to increase NA synthesis and turnover (Kety *et al.*, 1967; Modigh, 1976), decrease NA uptake into cortical

homogenates (Hendley and Welch, 1975; Minchin *et al.*, 1983), and increase the activity of the rate-limiting enzyme tyrosine hydroxylase (Mussachio *et al.*, 1969). Attenuation of clonidine-induced sedation (Heal *et al.*, 1981), clonidine-induced decrease in brain MOPEG-SO_4 concentration (Heal *et al.*, 1981), and clonidine-induced hypothermia (Pilc and Vetulani, 1982) have all been demonstrated following repeated ECS. The effects of ECS on clonidine-mediated responses suggest that repeated ECS may induce subsensitivity of inhibitory presynaptic receptors subserving NA release (Langer, 1979).

In the light of these findings, it was of interest to study the effect of repeated ECS on mechanisms involved in NA release. Chronic monoamine oxidase (MAO) inhibition with clorgyline has recently been shown to increase NA release from a rat brain cortical vesicular preparation and to markedly decrease the inhibition of NA release caused by the selective agonist clonidine (Cohen *et al.*, 1983). Changes in presynaptic release mechanisms may precede and partially mediate postsynaptic reduction in receptor number (Wolfe *et al.* 1978). We therefore examined the effect of repeated ECS on presynaptic release of NA from a rat brain cortical vesicular preparation in the presence or absence of clonidine (Ebstein *et al.*, 1983). A gravity-flow perfusion technique recently described by Ebstein *et al.* (1982) was used.

Effect of Single ECS

Animals were sacrificed 24 hr after a single ECS and K^+-evoked ^{3}H-NA release was determined in the presence and absence of clonidine which activates inhibitory presynaptic α_2-receptors (De Potter *et al.*, 1971; Starke, 1971; Langer, 1979). There was no difference at either 0.1 mM or 0.2 mM $CaCl_2$ in K^+-evoked ^{3}H-NA release between a cortical vesicular preparation obtained from ECS and sham-treated animals (Table I). At 0.1 mM and 0.2 mM $CaCl_2$, clonidine significantly inhibited K^+-evoked release of ^{3}H-NA. The magnitude of clonidine inhibition was similar in cortical vesicles obtained from ECS and sham-treated animals.

Effect of Chronic ECS

Animals were sacrificed 24 hr after the last of a series of 10 daily ECS. At 0.1 mM $CaCl_2$ there was a small but significant increase in K^+-evoked release of ^{3}H-NA in vesicles obtained from ECS-treated animals in the absence and presence of clonidine (Table II). In vesicles obtained from sham-treated animals, 50 and 250 nM clonidine significantly inhibited ^{3}H-NA release whereas in vesicles obtained from ECS-treated animals, significant inhibition by clonidine was observed only at 250 nM clonidine. At 0.2 mM and 1.0 mM $CaCl_2$ K^+-evoked

Table I. Effect of Single ECS on K^+ Evoked [^{3}H] Efflux from Rat Cerebral Cortical Vesicular Preparations[a]

	[^{3}H] efflux (count/min) ECS			[^{3}H] efflux (count/min) Sham		
		Clonidine nM[b]			Clonidine nM[b]	
$CaCl_2$ mM	Control	50	250	Control	50	250
0.1	887 ± 80 (15)	538 ± 59** (15)	634 ± 68* (15)	831 ± 87 (12)	617 ± 87 (11)	467 ± 50** (12)
0.2	3593 ± 195 (15)	2371 ± 174*** (15)	2292 ± 181*** (15)	3308 ± 276* (15)	2251 ± 221* (15)	2414 ± 246* (15)

[a]The KCl concentrations was 18.4 mM. The numbers in parentheses are the number of separate columns measuring [^{3}H] efflux in vesicles obtained from ECS and sham-treated animals.
[b]Effect of clonidine (50 and 250 nm) in [^{3}H] efflux in ECS or Sham groups *vs.* control [^{3}H] efflux in ECS or Sham groups: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$. Effect of ECS on [^{3}H] efflux in the absence or presence of clonidine 50 and 250 nM *vs.* effect of Sham on [^{3}H] efflux in the absence or presence of clonidine: no significant differences.

Table II. Effect of ECS x 10 on K+-Evoked [^{3}H] Efflux From Rat Cerebral Cortical Vesicular Preparations[a]

	[^{3}H] efflux (count/min) ECS			[^{3}H] efflux (count/min) Sham		
		Clonidine nM[b]			Clonidine nM[b]	
$CaCl_2$ (mM)	Control	50	250	Control	50	250
0.1	1350 ± 85[c] (18)	1071 ± 125[c] (18)	937 ± 157[c,*] (18)	1076 ± 70 (54)	710 ± 108** (18)	564 ± 113** (17)
0.2	1614 ± 170 (17)	1433 ± 121[c] (18)	1001 ± 147* (16)	1368 ± 177 (12)	983 ± 82 (12)	847 ± 121* (12)
1.0	4554 ± 227 (18)	3353 ± 207*** (18)	3387 ± 234** (17)	4252 ± 336 (17)	2778 ± 327** (18)	2723 ± 283** (16)

[a]The KCl concentration was 18.4 nM. Values are mean ±SEM. Numbers in parentheses are the numbers of separate columns measuring [^{3}H] efflux in vesicles obtained from ECS and Sham-treated animals.
[b]Effect of clonidine (50 and 250 nM) on [^{3}H] efflux in ECS or Sham groups *vs.* control [^{3}H] efflux in ECS or Sham groups: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.
[c]Effect of ECS on [^{3}H] efflux in the absence or presence of clonidine 50 and 250 nM *vs.* effect of Shan on [^{3}H] efflux in the presence or absence of clonidine: $p < 0.05$.

^{3}H-NA release was slightly greater in vesicles obtained from ECS-treated animals but this small difference was not significant (except at 0.2 mM $CaCl_2$ and 250 nM clonidine concentration).

The effect of multiple ECS treatments on presynaptic release of ^{3}H-NA from rat cortical vesicular preparations was small. At low concentration of $CaCl_2$ there was a small (25%) but significant increase in K^+-evoked NA release from vesicles obtained from chronically ECS-treated animals. After a single ECS, no effect on NA release was observed.

Minchin *et al.* (1983) reported no effect of repeated ECS on release of NA from rat cortical slices. The experiments of Minchin *et al.* (1983) were carried out in the presence of 1.2 mM $CaCl_2$ and 40 mM KCl, conditions which have been shown to reduce the effectiveness of presynaptic α_2-receptors in inhibiting release of NA (De Langen and Mulder, 1980; Ebstein *et al.*, 1982). However, the results obtained in the current study at high external medium $CaCl_2$ concentration are in agreement with those reported by Minchin *et al.* (1983).

Increased ^{3}H-NA release following ECS could be due to a reduction in α_2-adrenergic binding sites reported by some investigators after repeated ECS treatment (Pilc and Vetulani, 1982; Stanford and Nutt, 1982). The finding is also consistent with the functional evidence of presynaptic α_2-adrenergic subsensitivity discussed above (Heal *et al.*, 1981; Pilc and Vetulani, 1982). However, in comparison to experiments where clorgyline, a specific A-type MAO inhibitor, was administered to rats (Cohen *et al.*, 1983), the effect of ECS on release of ^{3}H-NA from rat cortical vesicles is minimal. Cortical vesicles obtained from clorgyline-treated rats showed markedly enhanced release of NA over a range of $CaCl_2$ concentrations (0.05 mM to 1.0 mM) (Cohen *et al.*, 1983). In addition there was a near total escape from clonidine suppression in vesicles obtained from clorgyline-treated animals whereas in chronically ECS-treated rats there was only a partial reduction in clonidine inhibition.

Although chronic MAO inhibition and ECS both induce increased NA release, possibly through a mechanism involving presynaptic α_2-adrenergic receptors, the effect of repeated ECS on these specific presynaptic mechanisms is much weaker than that observed after chronic clorgyline administration. The precise role of presynaptic factors in the postsynaptic β-adrenergic subsensitivity induced by repeated ECS and in the antidepressant mechanism of ECT thus remains to be definitively established.

ECS AND DOPAMINE RECEPTORS

Clinically Equivalent ECS and DA-Mediated Behaviors

The effects of ECS on DA receptors have been studied by the use in animal models of behavioral responses to pharmacological manipulations which

stimulate DA systems and by direct radioligand binding to DA receptor sites. Studies on the effect of ECS on DA-mediated behaviors show that motor activity following tranylcypromine/L-dopa and methamphetamine (Evans *et al.*, 1976; Green *et al.*, 1977), methamphetamine and apomorphine-induced circling in rats with unilateral nigrostriatal lesions (Green *et al.*, 1977), and apomorphine-induced stereotypies (Modigh, 1979) were all increased by 7-10 daily ECS.

When we administered ECS according to a more clinically equivalent schedule (three ECS per week for 4 weeks), increased apomorphine-induced stereotypies could not be demonstrated (Lerer *et al.*, 1982). Apomorphine stereotypies, however, were increased in the same laboratory following a regimen of seven daily ECS (Globus *et al.* 1982). Green and Deakin (1980) have been able to demonstrate enhancement of apomorphine-induced total activity scores following a regimen of five ECS over 10 days. The slightly more frequent ECS dosage regimen of Green and Deakin (1980) compared to that used by Lerer *et al.* (1982) may be sufficient to explain the discrepant observations. It should also be noted, however, that Green and Deakin (1980) measured total motor activity while Lerer *et al.* (1982) rated stereotyped behavior. Apomorphine-induced motor activity is thought to be mediated via nucleus accumbens and apomorphine-induced stereotypy via the stratum (Kelly *et al.*, 1975). The apparent discrepancy between the findings of Green and Deakin (1980) and those reported by Lerer *et al.* (1982) may therefore reflect differences in site of mediation of the DA behaviors tested.

Prevention of Haloperidol-Induced DA Supersensitivity by ECS

Behavioral DA supersensitivity following 7-10 daily ECS has not been matched by parallel changes in DA receptor number, as measured by striatal ^{3}H-spiperone binding (Bergstrom and Kellar, 1979; Atterwill, 1980). Chronic Li has also been reported to induce no change in striatal DA receptor number (Pert *et al.*, 1978). However, Pert *et al.* (1978) reported that chronic pretreatment with Li prevented increases in apomorphine-induced stereotypy and striatal ^{3}H-spiperone binding induced by chronic haloperidol administration, extending a previous report by Klawans *et al.* (1977). Pert *et al.* (1978) suggested that Li may act therapeutically in affective disorders by stabilizing receptor sensitivity.

We tested the effect of concurrent ECS administration on haloperidol-induced DA receptor supersensitivity using the same model as reported by Pert *et al.* (1978). Rats were divided into four treatment groups receiving haloperidol, haloperidol + ECS, ECS only, or no treatment. Haloperidol was administered in finely ground rat pellets (0.01% by weight) for 4 weeks. Control animals received identical drug-free ground food. ECS was administered three times a week during the 4-week haloperidol feeding, giving a total of 12 treatments. Behavioral observations were performed after a 4-day washout period in which neither haloperidol nor ECS was administered. A parallel group of animals in

each treatment group was killed by decapitation after the 4-day washout period and the brains removed rapidly. Caudate nuclei were removed by dissection and immediately frozen at −70 C for ^{3}H-spiperone binding assay.

Figure 1 illustrates the results of the behavioral observations. ECS alone did not significantly alter stereotypy scores at any point in the time course. Haloperidol pretreatment induced a consistent and highly significant increase in apomorphine-induced stereotypy which was present throughout the 40-min observation period. Total stereotypy scores (sum of all ten observations) were 36.2 ± 0.9 (x ± SEM) for the haloperidol-treated rats *vs.* 21.1 ± 1.6 for the control animals ($p < 0.001$). Administration of ECS concurrently with haloperidol attenuated the haloperidol-induced increase in apomorphine stereotypies, this attenuation becoming more prominent in the last 12 min of the 40-min observation period. Total stereotypy score for haloperidol plus ECS (29.0 ± 2.2) was 48% lower than for haloperidol alone (36.2 ± 0.9, $p < 0.01$).

Table III illustrates the results of the ^{3}H-spiperone binding studies. A haloperidol-induced increase in DA receptor number was clearly evident. Concurrent ECS ameliorated the haloperidol-induced supersensitivity as it did in the

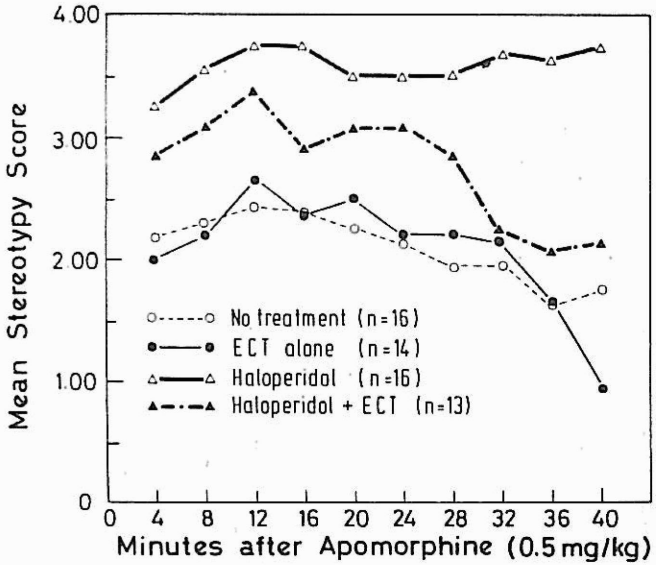

Fig. 1. Effect of ECS, haloperidol, and haloperidol + ECS on stereotyped behavior. Each point represents the mean stereotypy score for the animals in the treatment group at that time point. Behavioral observations were conducted in a darkened room by an observer blind to the treatment status of the animals. Apomorphine 0.5 mg/kg ip was injected to four animals at a time (one from each treatment group), who were then placed in identical wire observation cages. Stereotyped movements were observed and rated every 4 min for 1 min over a period of 40 min, using the scale of Kelly and Iversen (1976).

Table III. Effect of ECS on Haloperidol-Induced Biochemical DA Supersensitivity[a]

	Control (n = 13)	ECS (n = 13)	Haloperidol (n = 12)	Haloperidol + ECS (n = 11)
Bmax	43.5 ± 2.0	45.7 ± 2.4	67.5 ± 3.1[c]	58.9 ± 3.8[b]
Kd	0.67 ± 0.05	0.75 ± 0.05	0.84 ± 0.06	0.73 ± 0.07

[a] Effect of ECS, haloperidol, and haloperidol + ECS on ^{3}H-spiperone binding in the rat caudate nucleus. Bmax and Kd values represent mean ±SEM derived from 5-point Scatchard plot analysis. ^{3}H-Spiperone binding was determined by the method of Burt *et al.* (1977). Bmax and Kd values were determined from the Scatchard plot for each individual rat striatum. The plots were fitted with a computer program.
[b] $p < 0.001$ haloperidol *vs.* no treatment (Student's t test, two tailed).
[c] $p < 0.05$ haloperidol + ECS *vs.* haloperidol (Student's t test, one-tailed use because the biochemical hypothesis was defined after the behavior results has been obtained).

behavioral experiment. ECS alone induced no changes in dopamine receptor number. There was no difference in the K_D for spiperone (mean K_D = 0.75 nM) for the four groups.

These findings show ECS effects on changes in DA receptor sensitivity induced by haloperidol rather than direct effects of ECS on baseline DA receptor function and yielded parallel results with biochemical and behavioral methods. Chronic haloperidol induced a 72% supersensitivity of DA receptors as measured behaviorally, 48% of which was prevented by ECS. The biochemical supersensitivity was 55%, 36% of which was prevented by ECS. Although the biochemical effect was significant only at $p < 0.05$ (one-tailed) it is the direction of the behavioral findings and was derived from full Scatchard analysis for each of the animals. ECS did not significantly affect weight gain in the haloperidol-treated animals so that the ECS prevention of haloperidol-induced supersensitivity was unlikely to be due to reduced haloperidol intake.

Relevance to Mechanism of Action of ECT and Lithium

ECT and Li share a similar therapeutic profile characterized by a unique bidirectional clinical efficacy in affective disorder. ECT is a treatment of choice for severe depressions (Kendall, 1981), is effective in mania (McCabe, 1976), and may have prophylactic efficacy for recurrent affective episodes (Stevenson and Geoghegan, 1951; Karliner and Werheim, 1965). Li is uniquely antimanic (Shopsin *et al.* 1965), possibly antidepressant (Mendels, 1976), and highly effective in preventing affective decompensation in bipolar and possibly unipolar pa-

tients (Prien *et al.*, 1974). The parallels between the clinical profiles of these two very different treatments justify a search for mechanisms of action which they may have in common.

The findings reported above suggest a parallel effect of ECS and Li in preventing haloperidol-induced DA receptor supersensitivity. Prevention of induced supersensitivity by Li has been extended from the DA system to the NA and cholinergic systems. Li appears to have little or no effect on β-adrenergic receptor binding in rat cortex (Treiser and Kellar, 1979; Maggi and Enna, 1980). Treiser and Kellar (1979), however, have shown that chronic Li pretreatment prevented reserpine-induced increases of β-adrenergic receptor number. Reserpine-induced supersensitivity of β-adrenoceptor-linked NA-sensitive adenylate cyclase is similarly prevented by concurrent chronic Li administration (Lerer *et al.*, 1980a). ECS has also been shown to prevent reserpine-induced supersensitivity of NA-sensitive adenylate cyclase (Vetulani and Sulser, 1975) and to reverse reserpine-induced increases in β-adrenergic receptor number (Kellar *et al.*, 1981). Both Li and ECS have been shown to prevent hypoactivity induced in rodents by concurrently administered reserpine (Hendley and Welch, 1975; Lerer *et al.*, 1980b).

In the cholinergic system, Li has little or no direct effect on quinuclidinyl benzilate (^{3}H-QNB) binding in rat brain (Maggi and Enna, 1980; Levy *et al.*, 1982). However concurrent Li treatment prevented denervation-induced increases in junctional acetylcholine receptors (Pestronck and Drachman, 1980) and blocked atropine-induced increases in ^{3}H-QNB binding in whole brain (Levy *et al.*, 1982). ECS has now also been shown to prevent atropine-induced increases in ^{3}H-QNB binding in rat brain (see below).

Further parallels thus exist between the actions of ECS and Li which suggest that stabilization of receptor sensitivity may be a mechanism relevant to the therapeutic actions of both treatments. There are however some drawbacks to this hypothesis.

1. In comparing ECS and Li effects in the NA and cholinergic systems the direct effect of ECS to down-regulate β-adrenergic and cholinergic receptors should be noted, whereas the direct effect of Li on these receptors is minimal or absent (Maggi and Enna, 1980; Levy *et al.*, 1982).

2. The finding that concurrently administered Li prevents behavioral DA supersensitivity has been more consistently replicated (see Bunney and Garland, 1983) than the reported prevention of biochemical supersensitivity which at least two groups have been unable to find (Staunton *et al.*, 1982; Reches *et al.*, 1982). It may be noted in this context that the effect of ECS to prevent haloperidol-induced increases in apomorphine-induced stereotypies was also stronger than its effect to attenuate the haloperidol-induced increase in ^{3}H-spiperone binding.

3. Rosenblatt *et al.* (1980) have suggested that Li may in fact induce a down-regulation of striatal DA receptors which is demonstrable in the course of Li administration and 1 day following Li withdrawal. Other authors have also reported that chronic Li decreases ^{3}H-spiperone binding (Wajda *et al.*, 1981), although Staunton *et al.* (1982) found no effect. An effect of Li to down-regulate ^{3}H-spiperone-labeled striatal DA receptors might be the mechanism of stabilization by Li of DA receptors. However, this would not explain the ECS effect reported above, since ECS alone had no reported effect on ^{3}H-spiperone binding.

Prevention of receptor supersensitivity by Li nevertheless remains an heuristically attractive explanation for the prophylactic efficacy of Li in affective disorder. A prophylactic effect of maintenance ECT is also well recognized clinically but remains to be conclusively investigated (Steven and Geoghegan, 1951; Karliner and Weheim, 1965). It is possible that prevention of DA receptor supersensitivity may be a basic mechanism common to the prophylactic action of both Li and ECT. Neither Li nor ECS has been shown to reverse existing DA receptor supersensitivity (Klawans *et al.*, 1977; Globus *et al.*, 1981) so that a prophylactic role for this effect is the most plausible. Further studies are required to determine whether reported effects of Li (and ECS) to prevent induced changes in DA receptor sensitivity represent a robustly replicable explanation for their mechanism of action or an inconsistently observed artifactual effect common to both treatments.

ECS AND ACETYLCHOLINE RECEPTORS

Presynaptic Cholinergic Effects of ECS

Relatively few recent studies have examined the effects of repeated ECS on central cholinergic systems, which is surprising in view of the evidence for involvement of cholinergic neurons in seizure mechanisms and adaptive changes following convulsions (Fink, 1966; Karczmer *et al.*, 1973). Longoni *et al.* (1976) reported a significant decrease in acetylcholine content in the cerebral cortex immediately after a single electrically induced seizure. After daily ECS over 13 days, however, the change in cortical acetylcholine content was similar to that observed after only one ECS. Ictal and immediate postictal decreases in ACh content have also been reported by Richter and Crossland (1949), Takahashi *et al.* (1961), and Essman (1973).

Single ECS appears to increase choline acetyl transferase (ChAT) activity in cortex (Longoni *et al.*, 1976) and possibly other brain areas (Atterwill, 1983). This effect is transient, however, and no longer demonstable after a series of

ECS or drug-induced seizures (Longoni *et al.*, 1976; Atterwill, 1980, 1983). Acetylcholinesterase activity in rat brain is reported as increased by a single ECS (Adams *et al.*, 1969) but unchanged after repeated ECS (Pryor, 1974). Atterwill (1980) found no effect of single or repeated ECS on high-affinity choline uptake.

Repeated ECS thus appears to have no cumulative effect on the presynaptic cholinergic mechanisms studied. The results following single ECS, while variable, may be compatible with increased release of acetylcholine during the seizure. This possibility is supported by human data (Fink, 1966) showing increased CSF acetylcholine and choline levels following PTZ-induced or epileptic seizures. Release of acetylcholine during the seizure may have relevance to the cholinergic receptor changes following repeated ECS discussed below.

Down-Regulation of Muscarinic Cholinergic Receptors by ECS

We studied the effect of daily ECS for 7 days on muscarinic cholinergic receptors in rat cerebral cortex and hippocampus (Lerer *et al.*, 1983c). Rats were killed 24 hr after the last seizure and ^{3}H-QNB binding was assayed in the cortex and hippocampus. Binding of ^{3}H-QNB at 25 pM ^{3}H-QNB concentration was determined after the method described by Wastek and Yamamura (1978). As shown in Table IV, daily ECS for 7 days induced a statistically significant 15% and 13% decrease in ^{3}H-QNB binding in cortex and hippocampus, respectively. Scatchard analysis of binding data in cortex and hippocampus showed the ECS-induced decline in ^{3}H-QNB binding to be due to a reduction in receptor number only without change in affinity of the ligand for the ^{3}H-QNB binding site. Since ECS was found to have no effect on ^{3}H-QNB binding in cortex or hippocampus 24 h or 7 days after the seizure (Table IV). The latter time

Table IV. Effect of Single and Repeated ECS on Muscarinic Cholinergic Receptors in Rat Cerebral Cortex and Hippocampus[a]

	24 hr after ECS × 1 (% of control)	7 days after ECS × 1 (% of control)	24 hr after ECS × 7 (% of control)
Cortex	95 ± 5.8	108 ± 6.9	85 ± 4.4[b]
Hippocampus	103 ± 4.1	96 ± 10.0	87 ± 4.7[b]

[a] Figures represent percentage of control ^{3}H-QNB binding at 25 pM QNB. Each value is the mean ± SEM for binding data from 8-12 separate animals. Two-tailed *t* tests were used for statistical comparisons which were done on raw data before conversion into percentages.

[b] ECS *vs.* control, $p < 0.05$.

frame was studied in view of reports (Chiodo and Antelman, 1980) that a single ECS followed by a delay may induce receptor sensitivity changes of the same order of magnitude as a series of ECS.

The results reported here demonstrate that chronic ECS significantly decreases muscarinic cholinergic receptor binding in rat cerebral cortex and hippocampus. These findings confirm and extend those of Dashieff *et al.* (1982) who found that four ECS daily over 4 days induced a significant 19-25% decline in ^{3}H-QNB binding in the dentate and hippocampal gyri, respectively. The findings of Kellar *et al.* (1981) are in the same direction as those reported here but of lesser magnitude. Following daily ECS for 14 days, Kellar *et al.* (1981) found a 7-9% decline in ^{3}H-QNB binding in hippocampus and cortex, respectively, which did not reach statistical significance. Deakin *et al.* (1982) found only a minimal reduction in ^{3}H-QNB binding.

The difference in the magnitude of the ECS effect reported here and that reported by Kellar *et al.* (1981) and Deakin *et al.* (1982) may be methodological in origin and may derive from the higher ligand concentration (0.2 nM QNB and 2 nM QNB, respectively) used by these authors compared to the lower ^{3}H-QNB concentration used in the present study (0.025 nM QNB). McKinney and Coyle (1982) reported the existence of higher and low affinity muscarinic binding sites in rat cerebral cortex which are differentially up- or down-regulated by cholinergic input as well as by pharmacologic manipulations. Differences in ^{3}H-QNB concentrations used in binding assays may thus be responsible for the variability in the extent of down-regulation of ^{3}H-QNB binding sites following chronic ECS.

Prevention of Atropine-Induced Cholinergic Supersensitivity by ECS

It was of interest to determine whether down-regulation of muscarinic cholinergic receptors by ECS could also be demonstrated in the case of receptors rendered "supersensitive" by concurrent administration of a cholinergic antagonist (Lerer *et al.*, 1983c). This was achieved by administering atropine (10 mg/kg ip) daily for 5 days, from Day 2 to Day 5 of a 7-day ECS (or sham ECS) schedule. Control rats received vehicle injections (normal saline) according to the same schedule. Decapitation was 48 hr after the last atropine or vehicle injection (24 hr after the last ECS).

Atropine treatment resulted in a statistically significant increase in ^{3}H-QNB binding in cortex. This increase was reduced to control levels by concurrent ECS administration. Cortical ^{3}H-QNB binding in rats receiving ECS alone, however, was still significantly lower than in the group receiving ECS and atropine concurrently (Fig. 2).

The prevention by concurrent ECS of atropine-induced increases in ^{3}H-QNB binding reported here provides further support for a down-regulation by

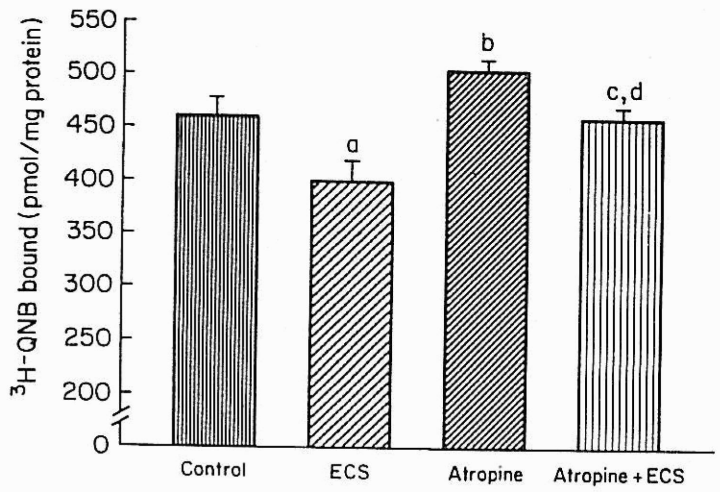

Fig. 2. Effect of ECS, atropine, and atropine + ECS on muscarinic cholinergic receptors in rat cerebral cortex. Bars represent mean ± SEM ^{3}H-QNB bound at 25 pM (QNB). One-way ANOVA ($F = 7.31$, $p < 0.01$) and t test were used for statistical comparisons (number of observations given in parentheses): a. ECS (10) *vs.* control (11), $p < 0.05$; b. atropine (11) *vs.* control (11), $p < 0.05$; c. atropine + ECS (9) *vs.* atropine (11), $p < 0.05$; d. atropine + ECS (9) *vs.* ECS (10), $p < 0.05$.

chronic ECS of muscarinic cholinergic binding sites. Concurrent ECS reduced cortical ^{3}H-QNB binding in the atropine-treated animals to control levels but not to the level found in the animals administered ECS only, thus further supporting the likelihood of an opposite action by the two treatments at the level of the muscarinic cholinergic receptor. In this respect, the effect of ECS appears to differ from that reported for lithium by Levy *et al.* (1982) (see above, "Relevance to Mechanism of Action of ECT and Lithium") who found that chronic lithium, while itself inducing a small (6%) increase in ^{3}H-QNB binding, blocked the increase in ^{3}H-QNB binding caused by concurrent atropine administration.

Relevance to Antidepressant Mechanism of ECT

Reduction of muscarinic cholinergic receptor density by chronic ECS may be functionally related to the antidepressant efficacy of ECT. This possibility may be considered in the light of theories linking depression to cholinergic predominance (Janowsky *et al.*, 1972) as well as more recent findings of "supersensitivity" of cholinergically mediated REM sleep induction (Sitaram and Gillin, 1980) and increased fibroblast ^{3}H-QNB binding sites (Nadi *et al.*, personal communication) in depressed patients. Down-regulation of muscarinic cholinergic receptors by ECT may represent a correction of the hypothesized cholinergic supersensitivity associated with depression.

Relevance to Amnestic Effects of ECT

Recent advances in delineating the role of cholinergic mechanisms in normal and impaired memory suggest that a possible role for central cholinergic dysfunction in ECT-induced amnesia be considered. A link between brain cholinergic activity and memory is supported by studies in normal subjects which show that centrally acting anticholinergic agents impair memory functions while cholinergic precursors, cholinergic agonists, or acetylcholinesterase inhibitors enhance them (Sitaram *et al.*, 1978; David *et al.*, 1978). Postmortem findings have strongly linked the cognitive deficits of Alzheimer's disease to degeneration of cholinergic neurons in the nucleus basalis of Meynert and depletion of choline acetyltransferase activity and acetylcholine levels in the cortex (Bartus *et al.*, 1982). ECT-induced memory impairment may result from a reversible down-regulation of muscarinic cholinergic receptors in the cerebral cortex and hippocampus induced by repeated seizures. This muscarinic cholinergic subsensitivity may imply a functional reduction in neurotransmission through the affected cholinergic synapses.

An hypothesis linking ECT-induced amnesia to cholinergic receptor subsensitivity in cerebral cortex and hippocamus is compatible with the transient nature of most of the ECT-induced memory deficits. ECT-induced memory impairment is characterized by an anterograde amnesia which is no longer present by 4-6 weeks after the last treatment (Squire, 1977; Weeks *et al.*, 1980) and by retrograde deficits which are either fully recovered or minimally demonstrable after 6 months (Squire *et al.*, 1981; Squire and Chace, 1975). A gradual restoration of receptor number after cessation of the treatments could account for the improvement in memory function which occurs. Unlike Alzheimer's disease, where cholinergic neurotransmission is thought to be permanently reduced because of degeneration of presynaptic cholinergic neurons, restoration of function could be expected to occur in patients with ECT-induced amnesia following cessation of the treatments. The situation may be analogous to that occurring in Parkinson's disease and neuroleptic-induced parkinsonism. The clinically similar extrapyramidal syndromes have been attributed to degeneration of nigral dopaminergic neurons in Parkinson's disease and reversible blockage of postsynaptic striatal dopamine receptors in drug-induced parkinsonism. Thus, although the pathogenetic basis of the memory deficits in Alzheimer's disease and ECT-induced amnesia may be different, a functionally equivalent reduction in cholinergic neurotransmission may be common to both.

This hypothesis may be tested both clinically and in the laboratory. The time-course of memory deficits induced by chronic ECS in rodents should parallel the ECS-induced reduction in muscarinic cholinergic receptor density. It should be determined whether pharmacological attenuation of the ECS-induced seizures (e.g., by phenobarbital) would attenuate amnesia (and cholinergic receptor subsensitivity) induced by repeated ECS in rodents (as has been demonstrated in humans by Ottoson, 1960). Chemically induced convulsions, on the other hand, should induce both memory deficits and cholinergic receptor down-regulation. In humans, repeated seizures induced by the inhaled convulsant, fluorothyl, have been shown to induce cognitive impairment of a similar degree as that caused by bilateral ECT (Fink *et al.*, 1961). In patients, the effects of cholinergic agonists and antagonists on memory functions following ECT may be tested. Antagonists would be expected to further impair performance whereas agonists should improve it as in patients with Alzheimer's disease (Bartus *et al.*, 1982). Parallel studies may be conducted in rodents along with the effect of vasopressin and other memory-active peptides which have been preliminarily studied in ECT-induced amnesia in humans (Weingartner *et al.*, 1981; Lerer *et al.*, 1983b; D'Elia and Frederiksen, 1980a, 1980b).

An hypothesis linking ECT-induced amnesia to alterations in brain cholinergic function could represent an important heuristic step in further unraveling the role of acetylcholine in memory processes. Studies aimed at testing the hypothesis could generate data and possibly treatment approaches relevant not only to ECT-induced amnesia but also to the wider spectrum of memory disorders in which disturbed cholinergic function may play a role.

CONCLUSIONS

The effects of ECS on the three neurotransmitter-receptor systems studied do not definitely establish a mechanism for ECT or its adverse effects. The fact that these findings are derived from studies on ECS effects in "normal" rats mandates that caution be exercised in their application to ECT in depressed humans. Similarly, although control rats were subjected to "sham ECS," the effects of subthreshold shock and other procedures of a more stressful nature than handling and electrode application remain to be comprehensively explored. A number of implications for previously suggested mechanisms and newer approaches nevertheless emerge.

Further basic studies are clearly needed in order to advance the putative antidepressant and adverse mechanisms of ECT outlined here. Further studies evaluating effects of ECS in parallel with those of other effective antidepressant treatments represent a potentially fruitful approach. Human studies aimed at seeking critical support for ECS findings derived from animal studies

are also needed (Lerer and Sitaram, 1983). Studies on neurochemical effects of ECS in animal models of depression represent a link between these two approaches (Lewis and McKinney, 1976). Although ECS clearly affects more than one neurotransmitter-receptor system, the effects of repeated treatments are certainly not as generalized as might be predicted and more amenable to critical evaluation than might have been thought.

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